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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 10/015,822
Filing Date: December 10, 2001
Appellant(s): BAKER ET AL.

Panpan Gao
For Appellant

**EXAMINER'S ANSWER**

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

This is in response to the appeal brief filed 10 January 2008 appealing from the Office action mailed 12 April 2007.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

As discussed in the Appeal Brief, U.S. Serial Number 10/013,911 is directed to antibodies against the PRO1759 polypeptide, which is related to the instant application claiming PRO1759 polypeptides. Also as Appellant states, there are numerous applications relying upon the gene amplification assay for utility which are under similar rejections and/or appeals.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Bea, S. et al. "BMI-1 gene amplification and overexpression in hematological malignancies occur mainly in mantle cell lymphomas" Cancer Research 61: 2409-2412, 2001.

Bork, A., "Powers and pitfalls in sequence analysis: the 70% hurdle", Genome Research 10: 398-400, 2000.

Bork et al., "Go hunting in sequence databases but watch out for the traps", Trends in Genetics 12(10): 425-427, 1996.

Brenner, S.E., "Errors in genome function", Trends in Genetics 15(4): 132-133, 1999.

Doerks et al., "Protein annotation: detective work for function prediction", Trends in Genetics 14(6): 248-250, 1998.

Godbout, R. et al. "Overexpression of a DEAD box protein (DDX1) in neuroblastoma and retinoblastoma cell lines" J. Biol. Chem. 273(33): 21161-21168, 1998.

Hanna, J.S. and Mornin, D. "HER-2/neu Breast Cancer Predictive Testing" Pathology Associates Medical Laboratories (1999), pp. 1-2.

Li, R. et al. "Identification of putative oncogenes in lung adenocarcinoma by a comprehensive functional genomic approach" Oncogene 25: 2628-2635, 2006.

Ngo et al., "Computational complexity, protein structure prediction, and the Levinthal paradox", in The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495, 1994.

Pennica, D. et al. "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors" Proc. Natl. Acad. Sci., 95: 14717-14722, 1998.

Sen "Aneuploidy and cancer" Curr. Opin. Oncol. 12: 82-88, 2000.

Skolnick et al., "From genes to protein structure and function: novel applications of computational approaches in the genomic era", Trends in Biotech 18(1): 34-39, 2000.

Smith et al., "The challenges of genome sequence annotation or "The devil is in the details"", Nature Biotech 15: 1222-1223, 1997.

Wells. J.A., "Additivity of mutational effects in proteins", Biochemistry 29 (37): 8509-8517, 1990.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

*35 U.S.C. § 101 (Utility)*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-35 and 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

The claims are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, or 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown of SEQ ID NO: 374, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 374, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203465; wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. It is noted that the phrase "wherein the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the claimed polypeptides be overexpressed in any tumor, or have any biological activity. The claims also recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide. The specification discloses the polypeptide of SEQ ID NO: 374 is also known as PRO1759. Appellant has gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 01 January 2008), p. 4, second paragraph of argument section.

At pages 494-508 of the specification, Example 143 discloses a gene amplification assay in which genomic DNA encoding PRO1759 had a ΔCt value of 1.11 to 1.51 for two out of twenty six lung tumor samples, and one out of twenty two colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 143 asserts that

gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the claimed polypeptides are useful as diagnostic agents or targets for therapeutic intervention in cancer (p. 494, lines 23-29; p. 508, lines 26-28). However, PRO1759 was reported as being amplified in significantly less than half of the lung and colon cancer samples tested. Therefore, if a new, putative lung or colon sample were tested for PRO1759 amplification, it is more likely than not that the PRO1759 diagnostic test would yield a false negative result.

Furthermore, the art recognizes that lung and colon epithelium is often aneuploid. Specifically, Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Aneuploidy is a feature of damaged tissue, and is commonly found in lung and colon tissues, which are subject to environmental influences. Such does not invariably lead to cancer; rather, the development of cancer is rare, as evidenced for example by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium or between colon cancer and normal colon samples, and does not correct for aneuploidy. Thus, it is not clear that PRO1759 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that PRO1759 is a diagnostic probe for lung cancer or a target for therapeutic drug development unless it is clear that PRO1759 is amplified to a clearly greater

extent in true lung tumor and colon tumor tissue relative to non-cancerous lung and colon epithelium.

Finally, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of lung and colon tumor samples had tested positive, the data have no bearing on the utility of the claimed PRO1759 *polypeptides*. In order for the PRO1759 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1759 mRNA or PRO1759 polypeptide levels in lung or colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Hanna and Mornin (1999, Pathology Associates Medical Laboratories), wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus, Hanna and Mornin provide evidence that the

level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1759 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

The *general* concept of gene amplification's lack of correlation with mRNA/polypeptide overexpression in cancer tissue is addressed by Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8), who teach a general lack of correlation between gene amplification and mRNA/polypeptide overexpression. The abstract of Godbout et al. teaches "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma (RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified.***" (emphasis added). The polypeptide encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not

overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1759 confers any growth advantage to a cell. For example, PRO1759 bears no significant sequence similarity with any previously characterized proteins known to play a role in cell division or cell survival. Thus, it cannot be presumed that the PRO1759 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified.

An additional reference that provides evidence that gene amplification does not generally lead to increased transcript is Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635). Li et al. used a functional approach that integrated simultaneous genomic and transcript microarray, proteomics, and tissue microarray analyses to directly identify putative oncogenes in lung adenocarcinoma. On page 2633, right column, Li et al. state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO1759.

Therefore, data pertaining to PRO1759 genomic DNA do not indicate anything significant regarding the claimed PRO1759 polypeptides. The data do not support the specification's assertion that PRO1759 polypeptides can be used as cancer diagnostics or therapeutic agents. Significant further research would have been required of the skilled artisan to reasonably confirm that the PRO1759 polypeptide is overexpressed in any cancer to the extent that the polypeptide could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1759 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1759 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejection (Pennica et al., Hanna and Mornin, Sen, Godbout et al., and Li et al.), the rejection is properly maintained.

*35 U.S.C. 112, first paragraph (Enablement)*

Claims 28-35 and 38-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-32 and 39-40 would remain rejected under 35 U.S.C. § 112, first paragraph.

The specification teaches that the term "'PRO/number polypeptide' and 'PRO/number' wherein the term 'number' is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (pg 301, lines 1-6). The PRO1759 nucleic acids and polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods (pg 301, lines 6-8). The specification discloses that a PRO polypeptide variant is defined as an active PRO polypeptide having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence, a full-length native sequence PRO polypeptide sequence lacking the signal peptide, an extracellular domain of a PRO polypeptide, with or without signal peptide, or any other fragment of a full-length PRO polypeptide sequence (pg 302, lines 4-32). However, the specification does not teach any variant, fragment, or derivative of the PRO1759 polypeptide other than the full-length amino acid sequence of SEQ ID NO: 374. The specification also does not teach functional or structural characteristics of the polypeptide variants, fragments, and derivatives recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally

possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

*35 U.S.C. 112, first paragraph (Written Description)*

Claims 28-32 and 39-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the claims are directed to an isolated polypeptide having at least 80%, 85%, 90%, 95%, or 99% amino acid sequence identity to (a) the amino acid sequence of the polypeptide shown of SEQ ID NO: 374, (b) the amino acid sequence of the polypeptide of SEQ ID NO: 374, lacking its associated signal peptide, or (c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203465; wherein the nucleic acid encoding the polypeptide is amplified in lung or colon tumors. The claims recite a chimeric polypeptide comprising a polypeptide fused to a heterologous polypeptide.

The specification discloses that a PRO polypeptide variant is defined as an active PRO polypeptide having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence, a full-length native sequence PRO polypeptide sequence lacking the signal peptide, an extracellular domain of a PRO polypeptide, with or without signal peptide, or any other fragment of a full-length PRO polypeptide sequence (pg 302, lines 4-32).

The claims of the instant application do not require that the polypeptides possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include actual reduction to practice, disclosure of drawings or structure chemical formulas, sufficient relevant identifying characteristics (such as, compete or partial structure, physical and/or chemical properties, and functional characteristics when coupled with a known or disclosed structure/function correlation), methods of making the claimed product, level of skill and knowledge in the art, predictability in the art, or any combination thereof. However, in this case, the only factors present in the claims are a partial structure in the form of a recitation of percent identity and a function of the nucleic acid sequence ("the nucleic acid encoding said polypeptide is amplified in lung or colon tumors"). There is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polypeptide species (SEQ ID NO: 374) is not adequate written description of an entire genus of

functionally equivalent polypeptides which incorporate all variants and fragments and with at least 80%, 85%, 90%, 95%, and 99% sequence identity to the polypeptide comprising the amino acid sequence of SEQ ID NO: 374.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "Appellant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated polypeptide consisting of the amino acid sequence of SEQ ID NO: 374, but not the full breadth of the claim meets the written description provision of 35

U.S.C. §112, first paragraph. Appellant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

**(10) Response to Argument**

**I. Rejection of claims 28-35 and 38-40 under the utility requirement of 35 USC §101**

From p. 4 to p. 6 of the Appeal Brief, Appellant provides a summary of their arguments. Appellant begins by reviewing the data presented in Example 143, which has been analyzed in detail in the rejection above. Specifically, Appellant argues that the skilled artisan would expect that the gene amplification data for PRO1759 gene implicates that the PRO1759 polypeptide is overexpressed. This has been fully considered but is not found to be persuasive because of the evidence that gene amplification is not correlated with polypeptide overexpression (Pennica et al., Hanna and Mornin, Godbout et al., Li et al., and Sen). Also, since the PRO1759 gene was only amplified at a ΔCt value of 1.11 to 1.51 for only two out of twenty six lung tumor samples, and only one out of twenty two colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers, if a new, putative lung or colon sample were tested for PRO1759 amplification, it is more likely than not that the PRO1759 diagnostic test would yield a false negative result.

At p. 5 of the Appeal Brief, Appellant refers to the Goddard declaration as evidence that gene amplification correlates with polypeptide overexpression. This has been fully considered

but is not found to be persuasive because it is not an accurate description of the Goddard declaration. The declaration addresses whether the ΔCt values are significant, and not whether or not gene amplification correlates with polypeptide levels. The Goddard declaration will be addressed in greater detail below, at the point in the arguments where Appellant provides more extensive arguments regarding the same.

At the second paragraph of p. 5 of the Brief, Appellant urges that Orntoft et al., Hyman et al., and Pollack et al. constitute evidence that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins (See abstract). It would appear that Appellant has provided no fact or evidence concerning a correlation between the instant specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1759 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide

levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At p. 5, paragraphs 3 and 4 through p. 6 of the Brief, Appellant refers to the Polakis declarations as evidencing that there is a general correlation between mRNA levels and polypeptide levels. Appellant refers to several publications relied upon by the examiner. Appellant urges that the examiner has withdrawn the assertion that mRNA levels are not predictive of polypeptide levels based on "Appellants' arguments and the overwhelming body of evidence in support of their position." Appellant concludes that the only remaining issue is whether or not DNA amplification correlates with mRNA expression. The examiner takes exception to this characterization of the prosecution history and remaining issues. In the interest of clarifying this for the Board, it is noted that the rejections were not withdrawn. Rather, the original version of the utility and enablement rejections relied upon three main issues: 1) whether genomic DNA levels were predictive of mRNA levels; 2) whether genomic DNA levels were predictive of polypeptide levels; and 3) whether mRNA levels were predictive of polypeptide levels. Many references were relied upon by both Appellants and the examiner to support their differing positions on these three issues. Over the course of prosecution, the examiner indicated that, upon further consideration, the basis for the rejections concerning issue 3) was withdrawn, and thus the references relied upon by the examiner and Appellant regarding issue 3) would no longer be addressed. However, the rejections themselves were not withdrawn, and are maintained based on issues 1) and 2) above. Please see p. 3 of the advisory action of 13

November 2007 for a complete explanation. The Polakis declarations will be addressed in detail later in this answer, at the point in the Brief where Appellant discusses the declarations in detail.

At p. 6 of the Appeal Brief, Appellant argues that the examiner applied an improper legal standard in that the examiner failed to establish, with evidence, that it is more likely than not that the PRO1759 polypeptide is not overexpressed in lung and colon cancer. This has been fully considered but is not found to be persuasive. The rejection relies upon several references evidencing that it is more likely than not that gene amplification is a result of non-specific aneuploidy and is not associated with mRNA or polypeptide overexpression. See Pennica et al., Hanna and Mornin, Godbout et al., Li et al., and Sen. Furthermore, the rejection is based upon the sound scientific reasoning that amplification in only two out of twenty six lung cancer samples and only one out of twenty two colon cancer samples indicates that it is more likely than not that a false negative result will be obtained by screening a new, putative lung or colon cancer sample with a PRO1759-based probe.

At the second and third paragraphs of p. 6 of the Appeal Brief, Appellant concludes that the references relied upon by the examiner do not suffice to make a *prima facie* case that more likely than not there is no general correlation between gene amplification and mRNA/polypeptide levels, and that a central dogma of molecule biology is that there is such a correlation. This has been fully considered but is not found to be persuasive. Based on the detailed consideration of the evidence of record (both supplied by Appellant and relied upon by the examiner), it is clear that it is more likely than not that a small gene amplification in a very small percentage of cancer samples does not impute a patentable utility on the encoded polypeptide, as will be established in this examiner's answer.

At the first and second full paragraphs of p. 7 of the Appeal Brief, Appellant urges that, based on the utility of PRO1759 polypeptides in diagnosis of cancer, one skilled in the art would know exactly how to use the claimed polypeptides for the diagnosis of cancer, without undue experimentation. This has been fully considered but is not found to be persuasive since the PRO1759 polypeptides do not have a patentable utility for reasons of record.

Appellant's detailed arguments begin at p. 7 of the Appeal brief. Appellant begins with a review of the legal standard for utility, with which the examiner takes no issue.

Beginning at p. 10 of the Brief, Appellant reviews Example 143, and refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 02 February 2005 is insufficient to overcome the rejection of claims 28-35 and 38-40 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.16 to 2.85 fold amplification in two out of twenty six lung cancer samples and one out of twenty two colon cancer samples is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO1759 polypeptides. The significance can be

questioned based on the weakness of the data and the strength of opposing evidence. In the instant case, only a very small percentage of the cancer samples tested positive for PRO1759 gene amplification. Also, the controls used were not matched, non-tumor lung samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

At pp. 11-12 of the Brief, Appellant argues that ample information has been provided on how to use the claimed PRO1759 polypeptides as diagnostic markers. Appellant characterizes amplification in a cancer sample as a biological activity. Appellant urges that ample evidence has been provided (Orntoft et al., Hyman et al., Pollack et al., Bea et al., Godbout et al., Ashkenazi declaration, Goddard declaration, Polakis I and II declarations) that it is more likely than not that, if a gene is amplified in cancer, the encoded polypeptide is also expressed at an elevated level. This has been fully considered but is not found to be persuasive. First, it is important to note that, while the specification makes general reference to diagnostic markers, there is no specific reference to diagnostic markers for specific cancers based on the gene amplification data in Example 143. Thus, there is no specific guidance regarding use of PRO1759 as a diagnostic marker for lung and colon cancer. Example 143 repeatedly states that

the data support a utility for a therapeutic agent. However, it is a long road between observance of an elevated level of a biological marker and a therapeutic agent. Even if the PRO1759 polypeptide were overexpressed in certain cancers, there is no evidence that inhibiting the biological activity would result in successful cancer treatment. There is no evidence, for example, that PRO1759 plays a role in oncogenesis or control of cell division.

Furthermore, as discussed above, gene amplification in only two out of twenty six lung tumor samples and only one out of twenty two colon tumor samples is not overwhelming. It is more likely than not that screening of a new, putative lung or colon cancer sample with a PRO1759-based probe would yield a false negative result. Orntoft et al., Hyman et al., and Pollack et al. are flawed as discussed at pp. 17-18 above. In fact, since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Godbout et al. make a strong case in favor of the rejection. Specifically, Godbout et al. state, "*It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell.*" There is no evidence or assertion of record that PRO1759 provides a selective growth advantage to a cell, and thus it cannot be presumed that the polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified. Regarding Bea et al., it is not unexpected that a putative oncogene that seems to participate in cell cycle regulation and senescence, when amplified in the genome, would also be amplified as mRNA and have correspondingly increased polypeptide expression. PRO1759 is not a putative oncogene, and the function of the encoded polypeptide is not known. Godbout et al. and Bea et al. clearly point out

that whether or not a polypeptide is over-expressed depends strictly upon the function of the polypeptide. The instant specification has not established that over-expression of PRO1759 polypeptide provides a growth advantage to a cell, and thus it cannot be said that Bea et al. and Godbout et al. constitute evidence to support Appellant's position. In fact, Godbout et al. and Bea et al. support the instant rejection. The Ashkenazi declaration supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. The Goddard declaration is silent with respect to whether or not gene amplification correlates with increased mRNA or polypeptide levels. Finally, the Polakis I and II declarations are limited to the issue of whether or not mRNA levels are predictive of polypeptide levels, which is no longer an issue in this rejection.

At p. 13 of the Appeal Brief, Appellant quotes the examiner and states that the examiner is factually incorrect. This has been fully considered but is not found to be persuasive. In the office action of 12 April 2007, the examiner very clearly and correctly indicated that Example 143 showed gene amplification in three samples total, representing two types of cancers. See pp. 4-5 of that action.

Appellant also argues that the examiner has applied a heightened utility standard, in that the gene amplification is significant. Appellant relies upon the Goddard declaration as supporting such. Appellant urges that the examiner has not provided any evidence that the amplification is not significant. This has been fully considered but is not found to be persuasive. The examiner's characterization of the amplification as "small" is based on comparison to other gene amplification levels. Even in the instant specification, many of the genes assayed and disclosed in Table 8 had ΔCT values well over those for PRO1759. For example, some of the

genes showed ΔCT values of up to 4.99, which would translate into an amplification of up to almost ten-fold. It is respectfully submitted that, if there is amplification of a gene in a single cell, the minimum amplification would be a doubling, or two-fold. Furthermore, the examiner maintains that gene amplification in only two out of twenty six lung cancer samples and only one out of twenty two colon cancer samples indicates that it is more likely than not that assaying a new, putative lung or colon cancer sample with a PRO1759-based probe would result in a false negative result.

At the top of p. 14 of the Appeal Brief, Appellant argues that amplification of the nucleic acids in even one lung or colon tumor provides specific and substantial utility for the nucleic acid as a diagnostic marker for the type of lung or colon tumor in which it was amplified. Appellant argues that the tumor samples listed in Table 8 represented various types/classes of lung and/or colon tumors at different stages. Appellant concludes that a positive result in one sample and not others indicates that the nucleic acid can be used as a marker for that particular kind of tumor. This has been fully considered but is not found to be persuasive. PRO1759 gene was reported as being amplified in samples HF-000840, HF-000795, and HF-001296. There is no detailed description of the type, class, or stage of any of these samples in the specification. At p. 499, information is given regarding types, classes, and/or stages of some of the samples, but not the samples in which PRO1759 tested positive for gene amplification. Beginning at p. 505 of the specification, a discussion and conclusion section is presented for the gene amplification Example 143. However, PRO1759 is not discussed in this section. From discussions of other genes, it was discovered that HF-000840 is a "primary lung tumor" sample and HF-000795 is a "colon tumor center" sample (see p. 507, line 9). The specification never provides a description

of HF-001296; however, Appellant has characterized this as a lung tumor sample in various remarks. Importantly, no information is provided regarding type, class, or stage of these cancer samples, and thus Appellant's argument holds no weight.

At pp. 14-16 of the Appeal Brief, Appellant reviews the statements provided in the Goddard declaration. The Goddard declaration under 37 CFR 1.132 filed 02 February 2005 is insufficient to overcome the rejection of claims 28-35 and 38-40 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.16 to 2.85 fold amplification in two out of twenty six lung cancer samples and one out of twenty two colon cancer samples is significant, and whether such data have any relevance to the claimed subject matter, i.e., PRO1759 polypeptides. The significance can be questioned based on the weakness of the data and the strength of opposing evidence. In the instant case, only a very small percentage of the cancer samples tested positive for PRO1759 gene amplification. Also, the controls used were not matched, non-tumor lung samples but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong

opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of polypeptide overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded polypeptides are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

At p. 16 of the Appeal Brief, Appellant argues that the pooled DNA controls are appropriate, making reference to the Bieche et al. and Pitti et al. publications. This has been fully considered but is not found to be persuasive. As has been previously argued on the record, neither Bieche et al. nor Pitti et al. assert that the genes disclosed therein are useful as diagnostic agents. Furthermore, there are many examples of publications wherein matched tissue samples are considered the standard for a proper control. See Pennica et al., Godbout et al., Li et al.

At p. 16 of the Appeal Brief, Appellant argues that only DNA levels were measured, not mRNA levels. Appellant concludes that the examiner's concern regarding whether or not genomic DNA or transcript levels were being measured is misplaced. This point is conceded. It is clear that Example 143 of the instant specification is directed to measurement of genomic DNA levels.

At p. 17 of the Appeal Brief, Appellant argues that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or aneuploidy. Appellant refers to the declaration of Dr. Ashkenazi in support of this position. This has been fully considered but is not found to be persuasive. As discussed above, Sen (2000, Curr. Opin. Oncol. 12:82-88) teaches that cancerous tissue is known

to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Aneuploidy is a feature of damaged tissue, and is commonly found in lung and colon tissues, which are subject to environmental influences. Such does not invariably lead to cancer; rather, the development of cancer is rare, as evidenced for example by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. The gene amplification assay in the instant specification does not provide a comparison between the lung tumor samples and normal lung epithelium or between colon cancer and normal colon samples, and does not correct for aneuploidy. Thus, it is not clear that PRO1759 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. One skilled in the art would not conclude that PRO1759 is a diagnostic probe for lung cancer or a target for therapeutic drug development unless it is clear that PRO1759 is amplified to a clearly greater extent in true lung tumor and colon tumor tissue relative to non-cancerous lung and colon epithelium.

At p. 18 of the Appeal Brief, Appellant argues that the examiner's requirement for structure/function data is not required for utility. Appellant also notes that selective advantage to cell survival is not the only mechanism by which genes impact cancer. This has been fully considered but is not found to be persuasive. As discussed above, the art indicates that only those amplified genes which confer a selective advantage on the cell is overexpressed in cancer cells. Godbout et al. (1998, J. Biol. Chem. 273(33):21161-8) state "The DEAD box gene, DDX1, is a putative RNA helicase that is co-amplified with MYCN in a subset of retinoblastoma

(RB) and neuroblastoma (NB) tumors and cell lines. ***Although gene amplification usually involves hundreds to thousands of kilobase pairs of DNA, a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified***." (emphasis added). The polypeptide encoded by the DDX gene *had been characterized* as being a putative RNA helicase, a type of enzyme that *would be expected to confer a selective advantage* to the cells in which it (the DDX gene) was amplified. On page 21167, right column, first full paragraph, Godbout et al. state "***It is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell*** (48, 49). For example, although ERBA is closely linked to ERBB2 in breast cancer and both genes are commonly amplified in these tumors, ERBA is not overexpressed (48). Similarly, three genes mapping to 12q13-14 (CDK4, SAS and MDM2) are overexpressed in a high percentage of malignant gliomas showing amplification of this chromosomal region, while other genes mapping to this region (GADD153, GL1, and A2MR) are rarely overexpressed in gene-amplified malignant gliomas (50, 51). The first three genes are probably the main targets of the amplification process, while the latter three genes are probably incidentally included in the amplicons." (emphasis added). There is no evidence in the instant application that PRO1759 confers any growth advantage to a cell, and thus it cannot be presumed that the PRO1759 polypeptide is overexpressed because the genomic DNA including the gene being studied is amplified. Li et al. (2006, Oncogene, Vol. 25, pages 2628-2635) state: "***In our study, 68.8% of the genes showing over-representation in the genome did not show elevated transcript levels***, implying that at least some of these genes are 'passenger' genes that are concurrently amplified because of their location with respect to amplicons but *lack biological relevance in terms of the*

*development of lung adenocarcinoma*." Since more than half of the amplified genes were not overexpressed, Li et al. constitutes strong evidence that ***it is more likely than not that gene amplification does NOT correlate with increased protein levels***, absent evidence that the polypeptide has biological relevance in cancer. There is no such evidence for PRO1759. Therefore, there is ample evidence that only those genes which confer a selective advantage to a cell are overexpressed in cancer cells. Regarding Appellant's statement that selective advantage to cell survival is not the only mechanism by which genes impact cancer, it is respectively submitted that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

At pp. 18-19 of the Appeal Brief, Appellant argues that the examiner has apparently not recognized that the claims are directed to antibodies, and not polynucleotides or polypeptides. This has been fully considered but is not found to be persuasive. The claims of the instant application are directed to PRO1759 *polypeptides* and the examiner has acknowledged such in all previous office actions. The prosecution history also clearly reflects the examiner's understanding that the claims are not directed to polynucleotides. Appellant also argues that the increase in PRO1759 genomic DNA is significant. Appellant quotes the M.P.E.P. and cautions the examiner not to interpret the phrase "immediate benefit to the public" to mean that products and services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. Appellant urges that the assertion of utility must be considered credible if it is directed to any particular practical purpose. Appellant again asserts that their

position is based on "overwhelming" evidence that gene amplification is more likely than not associated with polypeptide overexpression, and thus no further research is required. This has been fully considered but is not found to be persuasive. Patentable utility is a three-factored requirement: the utility must be specific, substantial, and credible. In the instant case, actual credibility has not been questioned. The rejection is based upon the asserted utility's failure to be substantial. M.P.E.P. § 2107.01 states that a "substantial utility" defines a "real world" use. Utilities that require carrying out further research to reasonably confirm a "real world" context of use are not substantial utilities. This section of the M.P.E.P. indicates that basic research such as studying the properties of the claimed product itself is a situation in which substantial utility is lacking. Such is exactly the situation in this application. The asserted utility for the claimed PRO1759 polypeptides is that they are useful as targets for cancer therapeutic agents for lung or colon cancer based on gene amplification data and, more generally, as diagnostic agents. The art clearly indicates that, more likely than not, gene amplification does not correlate with overexpression of the encoded polypeptide in the absence of information that said polypeptide confers a selective advantage to the cell. If the polypeptide is not overexpressed in cancer cells, it has no potential as a target to develop cancer therapeutics or diagnostics. Therefore, the skilled artisan *must* perform further experiments *on the claimed product* in order to "reasonably confirm" that it has a "real world" use as a cancer therapeutic or diagnostic.

Beginning at p. 19 of the Appeal Brief, Appellant argues that a *prima facie* case of lack of utility has not been established. Appellant again urges that the proper legal standard is "more likely than not." Appellant criticizes Pennica et al. as being limited to individual WISP genes, and that no general trends can be concluded therefrom. Appellant points to the correlation

between WISP-1 gene amplification and polypeptide overexpression. This has been fully considered but is not found to be persuasive. The instant application also presents data from a single gene at a time and makes conclusions about gene products from genomic DNA data. Pennica et al. constitutes evidence that it cannot be assumed that amplified genomic DNA results in overexpressed gene product. Godbout et al. and Li et al. also provide evidence to this effect with respect to the general concept of whether or not gene amplification correlates with increased mRNA/polypeptide expression. Finally, Sen constitutes evidence that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer.

At p. 21 of the Appeal Brief, Appellant criticizes Li et al. Appellant urges that Li et al. acknowledge that their results differed from those of Hyman et al. and Pollack et al., and note that the difference may be due to different methodologies. Appellant refers to the supplemental information accompanying the Li et al. article, enclosed with the Brief. Appellants urge that Li et al. used an amplification copy ratio of only 1.4, which is not significant according to the Goddard declaration, and that a copy number of at least 2 was necessary. This has been fully considered but is not found to be persuasive. First, it is noted that Hyman et al. also found that less than half of the amplified genes were overexpressed at the mRNA level, even though they only investigated genes in genomic DNA regions that were amplified at least 2-fold (argued in more detail above), and thus Hyman et al. supports the examiner's position. Furthermore, Li et al. did not limit their studies to genes that were amplified at less than 2-fold. In fact, the supplemental information indicates that some of the samples were required to bind with a probe requiring at least 2-fold amplification:

> Genes with copy number ratio > 1.40 (representing the upper 5% of the CGH ratios across all experiments) were considered to be overrepresented. A genomic fragment that contained six or more adjacent probes showing a copy number ratio > 1.40, or a region with at least three adjacent probes with a copy number ratio > 1.40 **and no less than one probe with a ratio > 2.0**, were considered to be amplicons. (emphasis added, from 1st page of supplemental material)

At p. 22 of the Appeal Brief, Appellant asserts that the PTO is focusing on distinction without a difference. Appellant submits that the disclosed assay is a comparative one, where what is important is that a significant difference in expression between tumor and non-tumor tissue is (or is not observed). Appellant states that it is this difference that is demonstrated by the assay in Example 143. Appellant's argument has been considered but is not found to be persuasive. Specifically, Example 143 discloses a gene amplification assay in which genomic DNA encoding PRO1759 had a ΔCt value of 1.11 to 1.51 for two out of twenty six lung tumor samples, and one out of twenty two colon tumor samples when compared to a pooled control of *blood* DNA from several healthy volunteers. The gene amplification assay does not provide a comparison between the lung tumor samples and normal lung epithelium or between colon cancer and normal colon samples, and does not correct for aneuploidy. Thus, it is not clear that PRO1759 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium.

At p. 22 of the Appeal Brief, Appellant argues that it is "more likely than not" for amplified genes to have increased mRNA and protein levels. Appellant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidencing that, in general, gene amplification increases mRNA expression. This has been fully considered but is not found to be persuasive. As discussed above, Orntoft et al. could only compare the levels of about 40 well-resolved and

focused *abundant* proteins (See abstract). It would appear that Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded polypeptide. Hyman et al. found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1759 would be correlated with elevated levels of mRNA, much less polypeptide. Since Hyman et al. found that less than half of the amplified genes were overexpressed at the mRNA level, Hyman et al. supports the basis of the rejections that it is more likely than not that gene amplification *fails* to correlate with increased mRNA/polypeptide levels. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung or colon cancer.

At the fourth full paragraph of p. 22 of the Appeal Brief, Appellant relies upon the Polakis I and II declarations as teaching that there is a general correlation between increased mRNA levels and increased polypeptide levels. This has been fully considered but is not found to be persuasive. Again, as discussed above, the two Polakis declarations are limited to the issue

of whether or not mRNA levels are predictive of polypeptide levels, which is no longer an issue in this rejection.

At the bottom of p. 22 through the top of p. 23 of the Appeal Brief, Appellant points to a recent Board decision reversing the examiner in a microarray case. Appellant quotes the decision that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." Appellant urges that there is a similar situation in the instant application wherein the Examiner has not presented any evidence specific to the PRO1759 polypeptide to refute Appellant's assertion of a correlation between DNA levels and mRNA/polypeptide levels. This has been fully considered but is not found to be persuasive. The fact pattern in the case at issue in the Board decision differs significantly from the fact pattern in the instant case. In the microarray case decided by the Board, there were several critical pieces of evidence supporting Appellant's position in addition to the assertion in the specification that increased mRNA levels correlated with increased polypeptide levels. In particular, there were multiple declarations submitted under 37 C.F.R. § 1.132, including highly probative declarations containing further data. In the instant case, the preponderance of the evidence does not support the assertion in the specification that increased genomic DNA levels correlate with increased mRNA/polypeptide levels. Indeed, the Ashkenazi declaration filed under 37 C.F.R. 1.132 on 02 February 2005 actually supports the Examiner's position.

At the top of p. 23 of the Appeal Brief, Appellant summarizes that Orntoft et al., Hyman al., Pollack et al., and the Polakis and Scott declarations support their position that gene amplification influences gene expression at the mRNA and protein levels. This has been fully

considered but is not found to be persuasive. Based on the preponderance of the evidence as a whole, the rejections are being maintained. Specifically, the fact that PRO1759 was amplified in so few cancer samples, as well as the Pennica et al., Hanna and Mornin, Godbout et al., Li et al., Sen, and Hyman et al. publications, and finally the Ashkenazi declaration, all support the rejections. Appellant relies on Orntoft et al., Hyman et al., and Pollack et al., which are flawed for reasons extensively discussed herein. Appellant also relies on the Goddard, Polakis declarations, which do not speak to whether or not gene amplification correlates with increased mRNA or polypeptide levels, and thus are off-point. Thus, the preponderance of the evidence weighs in favor of the rejections. It is noted that there has been no submission of a Scott declaration in the instant application.

At pp. 23-24 of the Appeal Brief, Appellant again discusses the Orntoft et al., Hyman et al., and Pollack et al. references in detail. Specifically, Appellant criticizes the examiner's statement that the references did not look at polypeptide levels, reasoning that the Polakis declarations provide the connection to polypeptide levels. This has been fully considered but is not found to be persuasive. This was only one observation of the three references made by the examiner during prosecution history. Orntoft et al. does not clearly support Appellant's position. Specifically, Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time as was done in the instant application. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis

was not done for PRO1759 in the instant specification. That is, it is not clear whether or not PRO1759 is in a gene cluster in a region of a chromosome that is highly amplified. Pollack et al. also used a similar approach, and thus is similarly flawed. Hyman et al. used similar methodology and found that less than half of the highly amplified genes showed increased mRNA expression. Accordingly, if anything, Hyman et al. supports the examiner's position that it is more likely than not that gene amplification fails to correlate with increased mRNA expression.

At the bottom of p. 24 of the Appeal Brief, Appellant implies that the different methodology of Orntoft et al. is insignificant, since Orntoft et al. teach that, in general, chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. This has been fully considered but is not found to be persuasive. Orntoft et al. did not state that a *gene* that is amplified at least 2-fold is more likely than not to have increased mRNA expression levels. Rather, Orntoft et al. limited their statements to *chromosomal areas* with more than 2-fold increase in DNA. The instant specification did not use this approach, but rather looked at the genes one at a time, without consideration of whether or not they were from chromosomal areas showing at least 2-fold increase in DNA. As discussed above, Pennica et al. is an example of research wherein individual genes were studies, and no generalizations could be made.

At the second full paragraph at p. 25 of the Appeal Brief, Appellant argues that the fact that Orntoft et al. did not investigate lung or colon cancer samples, but rather compared invasive tumors to benign ones was a strength of their investigation. This has been fully considered but is not found to be persuasive. The examiner does not mean to imply that the findings of Orntoft et

al. were meaningless. Rather, that the findings were not directly on-point with the types of tissues and samples in which the PRO1759 gene was reported to be amplified. Taken with the facts that Orntoft et al. used different methodology, the observation was meant to illustrate that Orntoft et al. conducted a different sort of investigation than the one put forth in the instant specification.

At the middle of p. 25 of the Appeal Brief, Appellant takes issue with the examiner's characterization of the amplification disclosed in Orntoft et al. as "low" and point out that both Orntoft et al. and PRO1759 showed more than a 2-fold amplification. This has been fully considered but is not found to be persuasive. As stated above, the very least that a single gene in a single cell can be amplified is 2-fold. Other genes in Table 8 of the instant specification were amplified up to 10-fold. Furthermore, since Orntoft et al. only looked at relatively large chromosomal areas, the findings are not extendable to data collected from one gene at a time, wherein it is not know ether or not that gene is located in a chromosomal area experiencing amplification.

At pp. 25-26 of the specification, Appellant reviews Hyman et al. Quoting from Hyman et al., Appellant concludes that Hyman et al. demonstrates that gene amplification typically leads to overexpression. This has been fully considered but is not found to be persuasive. Again, Hyman et al. only looked at relatively large chromosomal areas, not individual genes. Furthermore, even the best figure provide by Hyman et al., 44%, is less than half. Thus, Hyman et al. supports the examiner's position that it is more likely than not that an amplified gene is *not* overexpressed at the mRNA level.

At p. 26 of the Appeal Brief, Appellant discusses Pollack et al. Appellant urges that Pollack et al. profiled DNA copy number alteration across 6,691 mapped human genes in breast cancer samples, and compared such to mRNA levels determined by microarray analysis. Appellant quotes from Pollack et al.'s conclusion of a strong correlation between highly amplified genes and elevated mRNA expression. This has been fully considered but is not found to be persuasive. As discussed above, Pollack et al. also used the CGH methodology, and thus restricted their investigation to genes that are located in relatively large chromosomal areas experiencing amplification. There is no evidence that the PRO1759 gene comes from such a chromosomal area. Furthermore, Pollack et al. limited their conclusion to the regions that were "highly amplified." Finally, it is interesting to note that Pollack et al. found correlations in their breast cancer samples, but referred to another investigative group that found very poor correlations in colon cancer samples. See bottom of right column of p. 12967 of Pollack et al. wherein they discuss Platzer et al. Also interesting is that Pollack et al. used a normal female leukocyte DNA control from a single donor rather than normal breast tissue (matched tissue control), whereas Platzer et al. compared colon cancer samples to normal colon epithelium.

At p. 27 of the Appeal Brief, Appellant refers to the Ashkenazi declaration. Appellant urges that simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification even if the protein is not overexpressed. Appellant further argues that this leads to a better determination of a suitable therapy. The Ashkenazi declaration under 37 CFR 1.132 filed 02 February 2005 is insufficient to overcome the rejection of claims 28-35 and 38-40 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action because the declaration supports the rejections in admitting that amplified genes

may not correlate with gene product overexpression. It is also important to note that the specification never suggests using such information for tumor categorization or to develop more suitable therapies. In fact, other than a general assertion that a polypeptide can be used therapeutically, no "suitable therapy" is suggested for cancers that may be represented by the samples assayed in the instant specification.

At pp. 27-28 of the Appeal Brief, Appellant addresses the Hanna and Mornin publication. Appellant reviews the disclosure of Hanna and Mornin, and argues that Hanna and Mornin support the Ashkenazi declaration. Appellant urges that the examiner has misread Hanna and Mornin, in that Hanna and Mornin clearly state that gene amplification and polypeptide expression generally correlate well. This has been fully considered but is not found to be persuasive. Hanna and Mornin provide an important example of a lack of correlation between gene amplification and mRNA/polypeptide overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus, Hanna and Mornin provide evidence that the level of polypeptide expression *cannot* be presumed, but rather *must* be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1759 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial.

At pp. 28-29 of the Appeal Brief, Appellant argues that the gene encoding PRO1759 polypeptide has been shown to be amplified in three lung and colon tumor samples, and conclude that the PRO1759 gene is a tumor-associated gene, in accordance with the findings in Hanna and Mornin. Appellant asserts that the majority of amplified genes also are overexpressed and therefore the skilled artisan would reasonably expect that PRO1759 polypeptide is overexpressed in the cancer samples. Appellant further argues that, even if PRO1759 polypeptides were not overexpressed, such serves to further characterize tumors and help the physician determine the best treatment modality. This has been fully considered but is not found to be persuasive. Hanna and Mornin constitute evidence that the skilled artisan would not assume that an amplified gene is also overexpressed at the polypeptide level, but rather that the polypeptide levels must be determined separately. The preponderance of the evidence clearly supports the examiner's position that gene amplification is more likely than not to *fail* to correlate with increased expression at the mRNA or polypeptide levels. See Pennica et al., Godbout et al., Li et al., Sen, and Hyman et al. publications.

In conclusion, the rejection is supported by the preponderance of the evidence. Regarding the gene amplification assay itself, it is noted that the assay did not correct for aneuploidy, which is a common feature of non-cancerous, damaged lung epithelium (evidenced by Sen). The specification does not assert a utility for PRO1759 as a biomarker for damaged, pre-cancerous tissue, and such is not a well-established utility. Gene amplification publications used matched tissue controls, unlike Appellant's (Pennica et al., Godbout et al., Li et al.). Contrary to Appellant's assertions, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al.,

Godbout et al., Hyman et al., and Li et al. A declaration setting forth the expert opinion of Dr. Ashkenazi (received 02 February 2005) contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Hanna and Mornin provide evidence that the level of polypeptide expression must be tested empirically to determine whether or not the polypeptide can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the polypeptide level of PRO1759 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for the claimed polypeptides is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1759 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. Even more research would be required of the skilled artisan to determine if the claimed PRO1759 polypeptides can be used as a target for cancer therapeutics, since there is no evidence that PRO1759 plays a role in cancer formation or progression, such that inhibiting PRO1759 would result in effective cancer therapy. In the absence of information regarding whether or not PRO1759 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1759 **polypeptides and antibodies** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an Appellant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

At p. 29 of the Appeal Brief, Appellant argues that the rejection of claims 28-35 and 38-40 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be reversed for the same reasons detailed in the arguments against the rejection of claims 28-35 and 38-40 under 35 U.S.C. § 101 for lack of utility. This has been fully considered but is not found to be persuasive for the reasons set forth above establishing that claims 28-35 and 38-40 define an invention that lacks patentable utility.

**II. Rejection of claims 28-35 and 38-40 under 35 USC § 112, 1st paragraph, enablement**

At p. 29 of the Appeal Brief, Appellant argues that the rejection of claims 28-35 and 38-40 under 35 U.S.C. § 112, first paragraph, for lack of enablement should be reversed for the same reasons detailed in the arguments against the rejection of claims 28-35 and 38-40 under 35 U.S.C. § 101 for lack of utility. This has been fully considered but is not found to be persuasive for the reasons set forth above establishing that claims 28-35 and 38-40 define and invention that lacks patentable utility.

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-35 and 38-40 would remain rejected under 35 U.S.C. § 112, first paragraph.

At p. 29 of the Appeal Brief, Appellant contends that the claimed variants all share the functional limitation, that "the nucleic acid encoding the polypeptide is amplified in lung or colon tumors". Appellant concludes that one of ordinary skill in the art would understand how to make and use the claimed polypeptides in the diagnosis of lung or colon tumors. Appellant argues that the specification describes methods for identifying genes which are amplified in lung or colon tumors. At p. 30 of the Brief, Appellant argues that the specification teaches specific parameters to be associated with the term "percent identity" and accordingly, one of skill in the art could identify whether the variant PRO1759 sequence falls within the parameters of the claimed invention. Appellant states that once such an amino acid sequence was identified, the specification sets forth methods for making, preparing, and testing the amino acid sequences. Appellant submits that biological activities, together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, is believed to sufficiently define the claimed genus, such that one skilled in the art would have known how to make and use the claimed polypeptide sequences without undue experimentation. Appellant cites M.P.E.P. § 2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers* 221 USPQ 1165, 1174.

Appellant's arguments have been fully considered but are not found to be persuasive. The broad brush discussion of making and screening for variants does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO1759 polypeptide of SEQ ID NO: 374 is disclosed. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For

example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such trial and error experimentation is considered undue. Certain positions in the polypeptide sequence are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). However, Appellant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the PRO1759 protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. A large quantity of experimentation would be required by the skilled artisan to generate the infinite number of derivatives recited in the claims and screen the same for activity. As was found in Ex parte Hitzeman, 9 USPQ2d

1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Furthermore, recitation of the phrase "the nucleic acid encoding the polypeptide is amplified in lung or colon tumors" in the claims is not adequate to describe the PRO1759 polypeptide or all possible variants that have at least 80%, 85%, 90%, 95%, and 99% homology to the PRO1759 polypeptide, because the recitation confers no biological activity, function, feature, or characteristic to the ***polypeptide*** itself. The encoding nucleic acid is a separate molecule.

**III. Rejection of claims 28-32 and 39-40 under 35 USC § 112, 1st paragraph, written description**

It is noted that at the bottom of p. 31 through p. 32 of the Appeal Brief, Appellant cites pertinent case law reviewing the legal standard of written description. The Examiner takes no issue with Appellant's general comments regarding the legal standard for written description.

At the middle of p. 31 and at p. 33 of the Brief, Appellant argues that the specification reports the reduction to practice of the amino acid sequence of SEQ ID NO: 374. Appellant points to pages of the specification for support of "native" sequences, methods to determine

percent identity, what changes can be made to a PRO sequence, and methods of making PRO sequences. This has been fully considered but is not found to be persuasive. The structure of SEQ ID NO: 374 has been provided, and has adequate written description. However, no other structures that are at least 80% identical to that of SEQ ID NO: 374 and which are encoded by a nucleic acid that is amplified in lung or colon tumors have been disclosed. Description of a single species is not representative of the claimed genus. The specification provides a broad brush discussion of making variant polypeptides, including a discussion of "conservative" amino acid substitutions. However, such is merely an invitation to experiment to find those which may be encoded by a nucleic acid that is amplified in lung or colon tumors. There is no detailed guidance regarding which parts of the PRO1759 structure of SEQ ID NO: 374 are critical, for example. With the exception of SEQ ID NO: 374, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

At p. 33 of the Brief, Appellant submits that the specification describes methods for the determination of percent identity between two amino acid sequences. At the bottom of p. 33 of the Brief, Appellant further submits that Example 143 of the present application sets forth an assay for determining whether a nucleic acid sequence which encodes a variant polypeptide is amplified. Appellant's arguments have been fully considered, but are not found to be persuasive for the following reasons. First, a method of calculating the percentage identity is not equivalent to a method of making and it does not provide description for the instantly claimed genus of PRO1759 polypeptide variants. Moreover, "make and test" is not the legal standard for adequate

written description. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

At the middle of p. 31 and at the bottom of p. 33 of the Brief, Appellant argues that the claims recite the function that the nucleic acid encoding the polypeptides is amplified in lung or colon tumors. Appellant points to Example 143 as providing guidance for determining whether or not a nucleic acid is amplified in lung or colon tumors. At p. 34 of the Brief, Appellant argues that the functional limitation clearly limits the structure of the variants in the obvious sense that a protein lacking any structural similarity with SEQ ID NO: 374 would not be expected to conserve the same function. Appellant also submits that it is not necessary that the functional limitation be directly linked to structure because the claims already provide a structural limitation, in requiring that the claimed variants have at least 80% amino acid sequence identity to SEQ ID NO: 374. Appellant claims only those proteins which meet both limitations of the claims, structural and functional. This has been fully considered but is not found to be persuasive. The examiner strongly disagrees with Appellant that "wherein, the nucleic acid encoding said polypeptide is amplified in lung or colon tumors" is a functional recitation *for the claimed polypeptides*. The recitation confers no biological activity, function, feature, or characteristic to the polypeptide itself. The encoding nucleic acid is a separate molecule. The skilled artisan cannot look at a variant PRO1759 polypeptide and determine whether or not the encoding nucleic acid is amplified in lung or colon tumors. There is no assay *that can be done on the polypeptide itself* that can tell the skilled artisan whether or not a variant PRO1759

polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors. The skilled artisan must first isolate the encoding nucleic acid for their variant and then test it. The instant specification simply does not disclose any PRO1759 variant polypeptides, whether or not they are encoded by nucleic acids that are amplified in tumors. The prior art shows that very closely related polypeptides have different patterns of expression in cancer, as do their mRNAs, and their genomic DNAs may or may not be amplified. See Pennica et al. and Hanna and Mornin.

At the bottom of p. 34 through p. 35 of the Brief, Appellant indicates that there is no "structure function" relationship provided in Example 9. Appellant also argues that Example 14 of the Synopsis of Application of Written Description Guidelines states that protein variants meet the requirements as providing adequate written description for the claimed invention if (1) the procedures for making variant proteins are routine in the art, (2) the specification provides an assay for detecting the functional activity of the protein, and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence. At the middle of p. 35 of the Brief, Appellant asserts that the procedures for making claimed variant proteins are well known in the art and described in the specification. Appellant also submits that the specification provides assays for detecting the recited functional activities of the claimed variants. Appellant's arguments have been fully considered but are not found to be persuasive. First, it is not clear what "Example 9" Appellant is referring to. The examiner has assumed that Appellant is referring to Examples 9 and 14 from the Written Description Guidelines published in 1999 because Examples 9 and 14 of the current Written Description Guidelines published in 2008 do not match the synopses described by Appellant. However, as discussed above, the recited functional limitation is not actually a functional limitation for the *claimed* subject matter,

i.e., the PRO 1759 polypeptide. There is no assay *that can be done on the polypeptide itself* that can tell the skilled artisan whether or not a variant PRO1759 polypeptide is encoded by a nucleic acid that is amplified in lung or colon tumors. Therefore, the claims are interpreted as reciting structure alone, with no function, and are not analogous to old Examples 9, 14. Additionally, the broad brush discussion of making and screening for variants in the instant specification does not constitute a disclosure of a representative number of members. No such variants were made or shown to have activity. Only the PRO1759 polypeptide of SEQ ID NO: 374 is disclosed.

At the middle of p. 35 of the Brief, Appellant concludes this section by urging that the rejection of claims 28-32 and 39-40 under 35 U.S.C. § 112, first paragraph be reversed. The Examiner believes that the rejections should be sustained for the reasons set forth above.

At the bottom of p. 35 of the Brief, Appellant concludes their argument by urging reversal of all the outstanding rejections of claims 28-35 and 39-40. The Examiner believes that the rejections should be sustained for the reasons set forth above.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

**(12) Oral Hearing**

It does not appear that Appellant has requested an oral hearing at this time. However, if an oral hearing is requested, the examiner requests the opportunity to present arguments at the hearing.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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